PATENT
Our Docket: P-LA 1245

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Border and Ruoslahti	)	Examiner: P. Gambel
Serial No.: 08/349,479	)	Group Art Unit: 1644
Filed: December 2, 1994	)	
For: INHIBITING TRANSFORMING GROWTH FACTOR β TO PREVENT ACCUMULATION OF EXTRACELLULAR MATRIX	)	

Commissioner of Patents
Washington, D.C. 20231

DECLARATION UNDER 37 C.F.R. § 1.131

Sir:

1. We, Erkki Ruoslahti and Wayne Border, are coinventors named on the above-identified patent application, which claims priority to United States application Serial No. 07/416,656 (hereinafter '656), originally filed on October 3, 1989.

2. We are both Medical Doctors and state herein under oath that we conceived, prior to December 22, 1988, the claimed methods of decreasing the TGF-β-induced production and deleterious accumulation of extracellular matrix associated with a pathology or a condition, including glomerulonephritis, adult respiratory distress syndrome, cirrhosis of the liver, and scarring, by contacting the affected tissue with an anti-TGF-β antibody. We diligently pursued, and conducted all experiments and work related to, the claimed invention in the United States starting prior to December 22, 1988, until the filing date of the above-identified application.

EXHIBIT 1

3. As evidence that we conceived the claimed methods prior to December 22, 1988, we enclose as Exhibit A, a Declaration under 37 C.F.R. § 1.132 by Lucia Languino, Ph.D., and as Exhibit B, photocopies of laboratory notebook pages from the laboratory notebook of Dr. Languino, one of which has attached to it a La Jolla Cancer Research Foundation animal procedure request form. The dates of the exhibits, all of which are prior to December 22, 1988, have been redacted; except for the La Jolla Cancer Research Foundation animal procedure request form included in Exhibit B, which indicates that the animals were bled for anti-TGF-β serum on December 13, 16, and 21 of 1988.

4. In Exhibit A, Dr. Languino indicates that, prior to December 22, 1988, we had asked for her assistance in the preparation of anti-TGF-β antibodies against amino acids 78 to 109 of TGF-β for a stated goal of using anti-TGF-β antibodies to inhibit TGF-β in order to decrease the deleterious TGF-β-induced production and accumulation of extracellular matrix (ECM) associated with a disease, including kidney disease.

5. Exhibit B contains two laboratory notebook pages and a La Jolla Cancer Research Foundation animal procedure request. The laboratory notebook pages from Dr. Languino's notebook, which are dated prior to December 22, 1988, set forth protocols for injection of rabbits with TGF-β peptides, including linear and cyclic TGF-β peptides, in order to prepare anti-TGF-β antiserum. The La Jolla Cancer Research Foundation animal procedure request form indicates that the animals were bled for anti-TGF-β serum on December 13, 16, and 21 of 1988. As

corroborated by Dr. Languino in Exhibit A, at the time the documents encompassed in Exhibit B were created, a stated goal of preparing anti-TGF-β antibodies was their use to inhibit TGF-β in order to decrease deleterious TGF-β-induced production and accumulation of extracellular matrix (ECM) associated with a pathology or condition, including glomerulonephritis, adult respiratory distress syndrome, cirrhosis of the liver, and scarring.

6. As further evidence of conception of the claimed methods, provided as Exhibit C is a conference abstract published for the Meeting of the American Society of Nephrology in San Antonio, Texas, which took place from December 11 to 14, 1988. This conference abstract, which lists us as first and senior authors, is entitled "Transforming Growth Factor β (TGFβ) Uniquely Regulates Production of Glomerular Extracellular Matrix." The conference abstract shows that we realized, prior to December 22, 1988, that "TGF-β is unique among growth factors in its metabolic effect on glomerular ECM" and that the release of TGF-β in glomerulonephritis could stimulate the expansion of ECM and progression to glomerulosclerosis. At the time this abstract was submitted, given our medical training as physicians, we already had conceived of using anti-TGF-β antibodies in order to decrease deleterious TGF-β-induced production and accumulation of extracellular matrix (ECM) associated with glomerulonephritis or other pathologies associated with TGF-β-induced expansion of the ECM.

7. As further evidence of conception of the claimed methods, and of our diligence in reducing the claimed methods to practice, provided as Exhibit D is a copy of portions (cover page and pages 13 and 27) of a Grant Application executed and submitted by Dr. Border on January 24, 1989. Section A.2.f. of page 13 of the Grant Application (Exhibit E), in the section related to a Research Plan-Specific Aim, in vivo, explicitly states that we contemplated "To develop regimens for therapeutic intervention in the disease model by antibodies and other agents capable of neutralizing the TGF-β effect." Paragraph "e." of page 27 of the Grant Application, in the section related to Experimental Design and Methods, explicitly states that:

> We have proposed several experiments that may provide agents that could block or ameliorate the action of TGFβ in the animal model of mesangial injury...It is conceivable that one or more of these agents could be administered to the animal and/or infused directly into the kidney as therapeutic agents to prevent the expansion of mesangial matrix...We expect that one or more of the agents to be tested will block the action of TGFβ. This information would be immediately applicable to the design of a study to treat humans with glomerulonephritis.

8. As further evidence of diligence in reducing to practice the claimed invention, we provide Exhibit E, which is copy of a portion (cover page, pages 2-5, 8 and 9) of an initial draft manuscript titled "An Antiserum Against Transforming Growth Factor β Suppresses Experimental Glomerulonephritis" as it existed in draft form on August 28, 1989. The draft manuscript summarizes results of numerous experiments conducted subsequent to the date of ordering the preparation of anti-TGF-β antibodies as set forth in Exhibits A and B, through the drafting of the manuscript on August 28, 1989. Exhibit E contains the *in vivo* protocol corresponding to Example VII of the specification, directed to treatment of anti-Thy-1-induced nephritic rats with control rabbit serum or anti-TGF-β serum and further states that acute glomerular disease can be effectively suppressed with anti-TGFβ treatment.

9. We do not know and do not believe that the invention was in the public prior to the time we conceived of the invention and reduced it to practice and we have never abandoned the application.

I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may

jeopardize the validity of the application or any patent issuing therefrom.

Respectfully submitted,

3-14-01
Date

Erkki Ruoslahti

Date

Wayne Border

jeopardize the validity of the application or any patent issuing therefrom.

Respectfully submitted,

Date

Erkki Ruoslahti

3/15/01
Date

Wayne Border